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(71) Applicant: NISSAN CHEMICAL INDUSTRIES LTD.
3-7-1, Kanda Nishiki-cho
Chiyoda-ku Tokyo (JP)

(72) Inventor: Seto, Kiyotomo Nissan Chemical Industries Ltd.
Chuo Kenkyusho 722-1, Tsuboi-cho
Funabashi-shi Chiba-ken (JP)

Tanaka, Sakuya Nissan Chemical Industries Ltd.
Seibutsukagaku Kenkyusho, No. 1470, Ooaza shiraoka
Minamisaitama-gun Saitama-ken (JP)

Sakoda, Ryozo Nissan Chemical Industries Ltd.
Chuo Kenkyusho 722-1, Tsuboi-cho
Funabashi-shi Chiba-ken (JP)

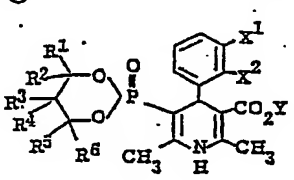
Sakai, Tosinori Nissan Chemical Industries Ltd.
Seibutsukagaku Kenkyusho, No. 1470, Ooaza shiraoka
Minamisaitama-gun Saitama-ken (JP)

Masuda, Yukinori Nissan Chemical Industries Ltd.
Seibutsukagaku Kenkyusho, No. 1470, Ooaza shiraoka
Minamisaitama-gun Saitama-ken (JP)

(74) Representative: Wächtershäuser, Günter, Dr.
Tal 29
D-8000 München 2 (DE)

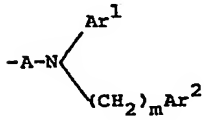
(54) Dihydropyridine-5-phosphonic acid cyclic propylene ester.

(57) A compound of the formula:

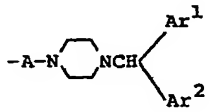


(I)

wherein each of R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different, is hydrogen or C_1-C_4 alkyl; one of X^1 and X^2 is nitro, fluorine, chlorine, difluoromethoxy or trifluoromethyl and the other is hydrogen, or both of X^1 and X^2 are chlorine; and Y is



wherein A is C_2-C_6 alkylene, each of Ar^1 and Ar^2 which may be the same or different, is phenyl which may be substituted by chlorine, fluorine or C_1-C_3 alkoxy, and m is an integer of from 0 to 4, or Y is



wherein A, Ar^1 and Ar^2 are as defined above when that both X^1 and X^2 are chlorine; or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt.

EP 0 230 944 A1

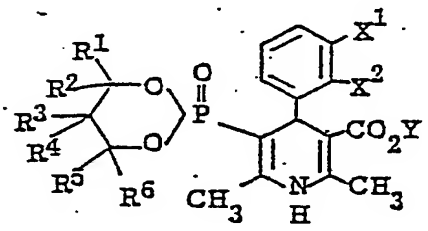
Description

DIHYDROPYRIDINE-5-PHOSPHONIC ACID CYCLIC PROPYLENE ESTER

The present invention relates to a novel 1,4-dihydropyridine-5-phosphonic acid cyclic propylene ester or its pharmaceutically acceptable salt, or a solvate of the ester or the salt, a process for the preparation thereof, and an antihypertensive agent or coronary or cerebral vasodilator composition containing the novel ester or its pharmaceutically acceptable salt, or a solvate of the ester or the salt.

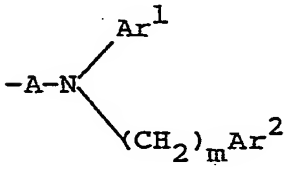
1,4-Dihydropyridines-5-phosphonic acid esters are known to be useful for the medical treatment of coronary heart diseases, cerebral diseases, hypertension or arrhythmia, as they are capable of inhibiting the contraction of smooth muscle and cardiac muscle by calcium antagonistic effects. (See European Patent Publications EP 0159040A, EP 0212117A, EP 0141222A and EP 0141221A, and Japanese Patent Publication 60-069089.)

The present invention provides a novel compound of the formula:

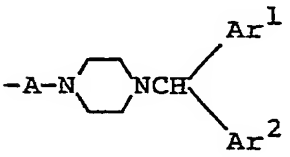


(I)

wherein each of R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different, is hydrogen or C_1-C_4 alkyl; one of X^1 and X^2 is nitro, fluorine, chlorine, difluoromethoxy or trifluoromethyl and the other is hydrogen, or both of X^1 and X^2 are chlorine; and Y is



wherein A is C_2-C_6 alkylene, each of Ar^1 and Ar^2 which may be the same or different, is phenyl which may be substituted by chlorine, fluorine or C_1-C_3 alkoxy, and m is an integer of from 0 to 4, or Y is



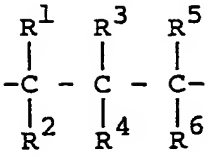
wherein A, Ar^1 and Ar^2 are as defined above when X^1 is hydrogen and X^2 is difluoromethoxy, or when both X^1 and X^2 are chlorine; or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt.

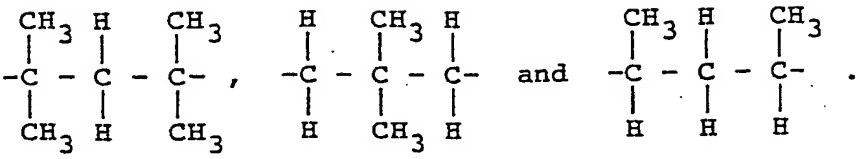
Some of the compounds of the formula I have optical isomers or diastereomers. The present invention covers such optical isomers and diastereomers.

The present invention also provides an antihypertensive agent or coronary or cerebral vasodilator composition comprising an effective amount of the compound of the formula I or its pharmaceutically acceptable salt, or a solvate of the compound or the salt, and a pharmaceutically acceptable diluent or carrier.

The substituents in the formula I of the compounds of the present invention will be further illustrated as hereunder.

Examples of R^1, R^2, R^3, R^4, R^5 and R^6 in the formula I are hydrogen, methyl, ethyl, n-propyl and i-propyl. And preferred examples of


in the formula I are



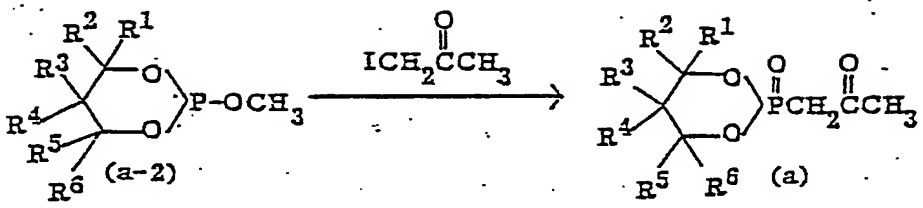
Examples of X^1 and X^2 in the formula I are hydrogen, nitro, chlorine, fluorine, difluoromethoxy and trifluoromethyl. Preferred examples of X^1 and X^2 in the formula I are hydrogen, nitro and chlorine.

Examples of A are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-C(CH_3)_2CH_2-$ and $-CH_2C(CH_3)_2CH_2-$. Preferred examples of A are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$.

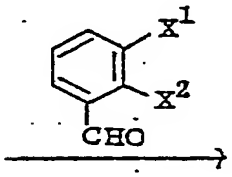
Examples of Ar^1 and Ar^2 are phenyl, fluorophenyl, chlorophenyl, dichlorophenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, ethoxyphenyl and diethoxyphenyl. Preferred examples of Ar^1 and Ar^2 are phenyl or p-fluorophenyl.

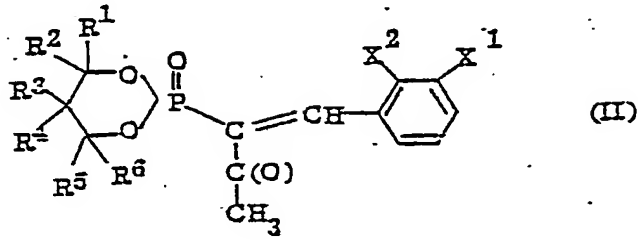
The compound of the present invention can be prepared in accordance with the flow chart of the following Scheme I.

(a)

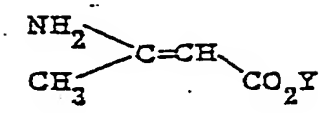


(a-2)



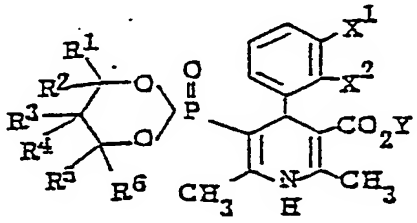


(II)

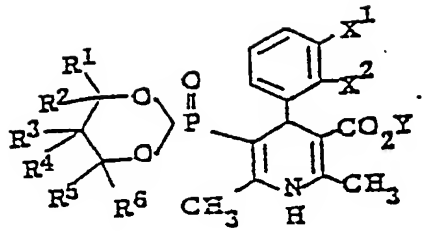


(III)

solvent

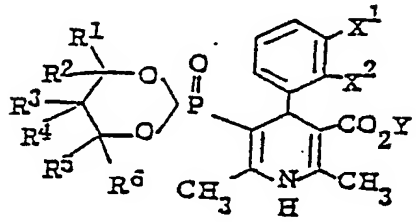


(I) or



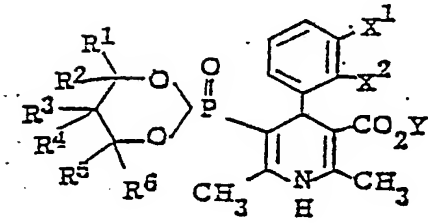
· solvent (VI)

acid
solvent →



· acid (IV)

or



· acid · solvent (V)

In Scheme I, R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and Y have the same meanings as defined with respect to the formula I.

The acetonyl phosphonic acid cyclic propylene ester (a) can be prepared by means of a conventional technique (see D.W. White, J. Am. Chem. Soc., 92, 7125-7135 (1970)). Namely, as shown by Scheme I, it is obtainable by the reaction of a 1-methoxy-1-phospha-2,6-dioxa cyclohexane derivative (a-2) with iodoacetone.

The compounds of the present invention of the formula I can be obtained by reacting the compound of the formula II with the compound of the formula III in an inert solvent in accordance with the above Scheme I. The starting compound of the formula II is obtainable by reacting the acetonyl phosphonic acid cyclic ester (a) with a benzaldehyde derivative by means of a conventional technique. Likewise, the starting compound of the formula III can readily be obtained by reacting the corresponding carbonyl compound with ammonia. The starting compound of the formula III may be formed in the reaction system simply by mixing the corresponding carbonyl compound with ammonia and is not necessarily required to be isolated.

The inert solvent includes an alcohol solvent such as methanol, ethanol, propanol or isopropanol, an ether solvent such as 1,2-dimethoxyethane or THF, an aromatic hydrocarbon solvent such as benzene, toluene or xylene, a nitrile solvent such as acetonitrile or benzonitrile, an amide solvent such as DAM, DMF or N-methylpyrrolidone, a sulfoxide solvent such as DMSO or sulfolane, an ester solvent such as ethyl acetate or butyrolactone, or pyridine.

The reaction is usually conducted at a temperature of from room temperature to 200° C, preferably from 60 to 140° C, for from 1 to 100 hours, preferably from 5 to 20 hours.

The resulting compound of the formula I may form a solvate of the formula VI depending upon the type of the solvent used or the type of the compound of the formula I. (See Example 13.)

The salt of the formula IV may be obtained by reacting a compound of the formula I or VI with an acid in the presence of an inert solvent. As the acid, there may be employed an acid capable of forming a pharmaceutically acceptable salt, such as hydrogen chloride, sulfuric acid, nitric acid, succinic acid, acetic acid or lactic acid. For the purpose of facilitating the purification of the compound of the formula I, however, it

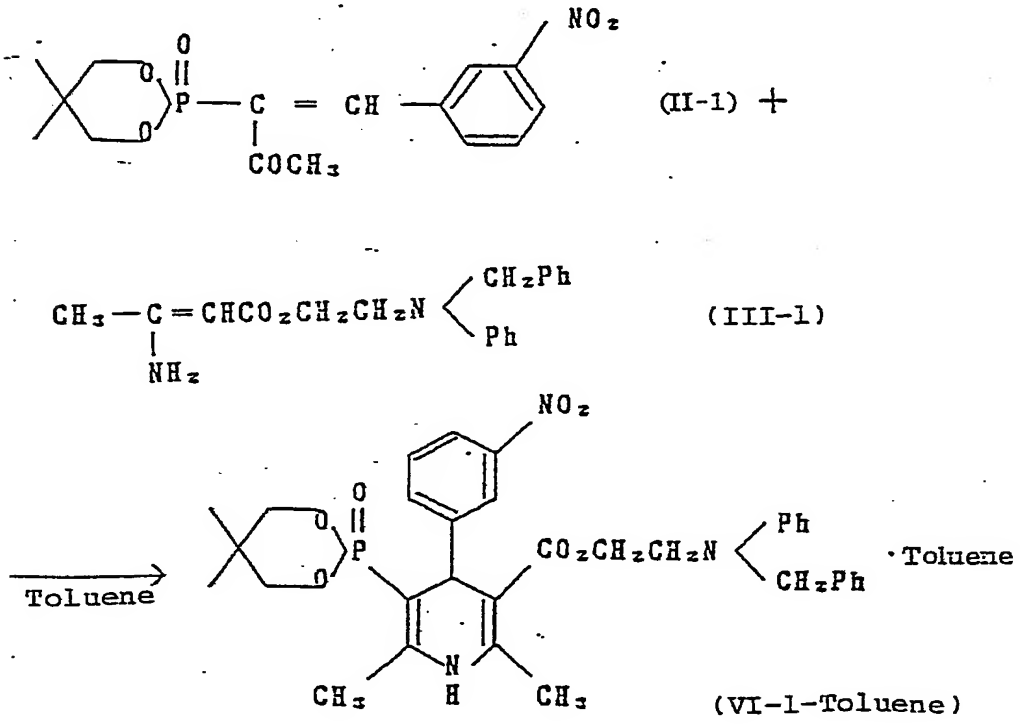
is possible to use other strong acids, such as hydrogen bromide, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid.

Depending upon the type of the compound of the formula I and the type of the solvent for the salt-forming reaction, it is possible that instead of a salt of the formula IV, a solvate of such a salt having the formula V forms. (See Example 14.)

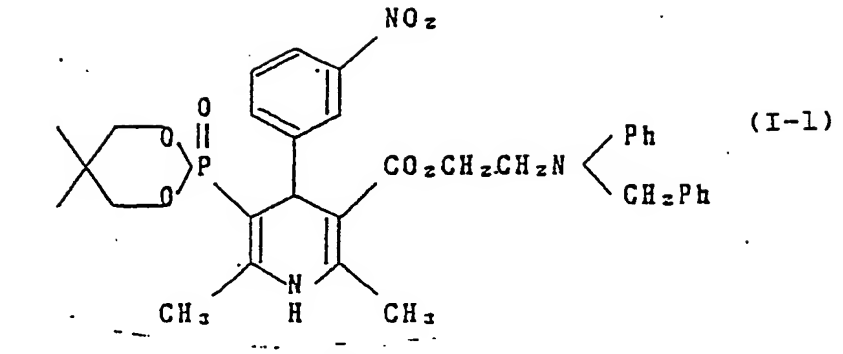
As mentioned above, the compound of the formula VI is a solvate of the compound of the formula I. As the solvent for such a solvate, benzene or toluene may be mentioned. Xylenes may also be useful as solvents for solvates.

Referring to the following Scheme 2, a solvate of the formula VI-I-Toluene is formed by the reaction of a compound of the formula II-I with a compound of the formula III-I in toluene, and precipitates. The solvate of the formula VI-I-Toluene is an adduct of 1 mol of the compound of the formula I-I with 1 mol of toluene. The solubility of this solvate in toluene is extremely low at a level of about 0.02% by weight at 20°C. Accordingly, it is possible to readily remove toluene-soluble impurities by precipitating the solvate from the toluene reaction solution, followed by washing with toluene. Further, it is possible to obtain the solvate in good yield from the toluene reaction solution, since the solvate has a low solubility in toluene.

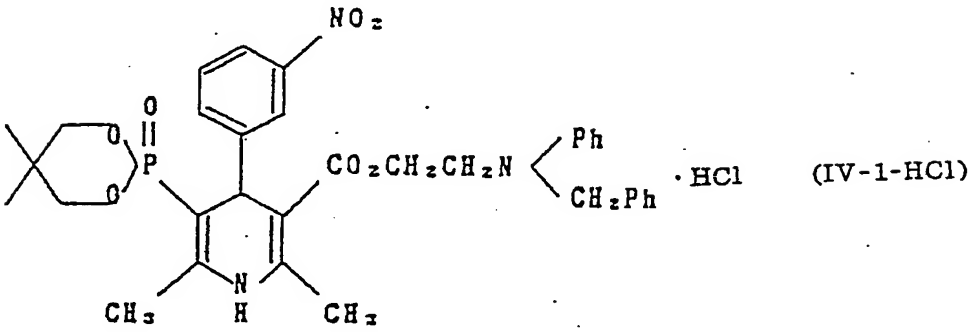
Scheme 2



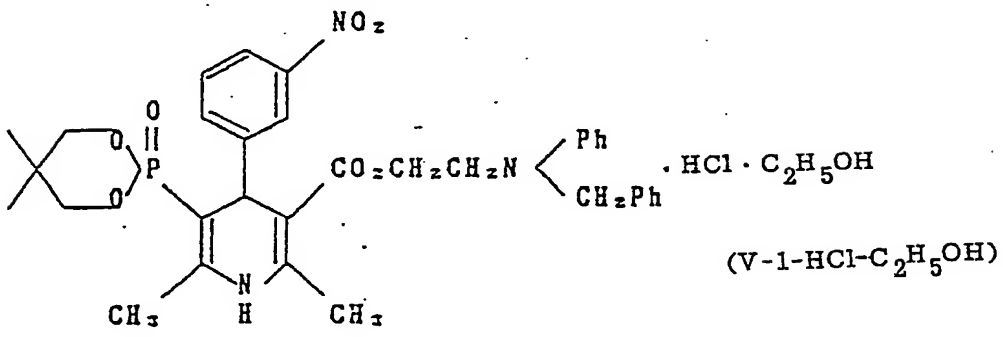
Further, by way of the solvate of the formula VI-I-Toluene, it is possible to readily obtain e.g. compounds of the following formulas I-I, IV-I-HCl and V-I-HCl-C_2H_5OH in high purity.



(I-1)



(IV-1-HCl)



(V-1-HCl-C_2H_5OH)

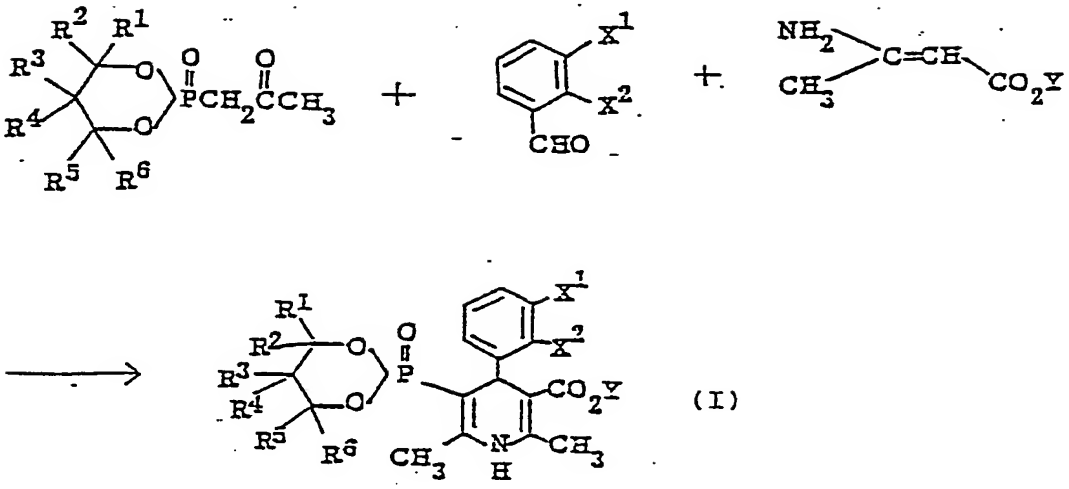
Namely, it is possible to obtain a compound of the formula I free from a solvent by recrystallizing the solvate of the formula VI from e.g. ethyl acetate or ethanol. For example, the compound of the formula I-1 can be obtained by recrystallizing the toluene solvate of the formula VI-1-Toluene from ethyl acetate or ethanol. (See Example 13.)

The hydrochloride of the formula IV-1-HCl has three types of crystal forms i.e. α-, β- and γ-forms. The difference between these crystal forms is shown by the difference in the manner for obtaining them as disclosed in Examples 15 and 16. It is also shown by the difference in the X-ray diffraction spectra. There is no pharmacological difference found among these three types of crystal forms.

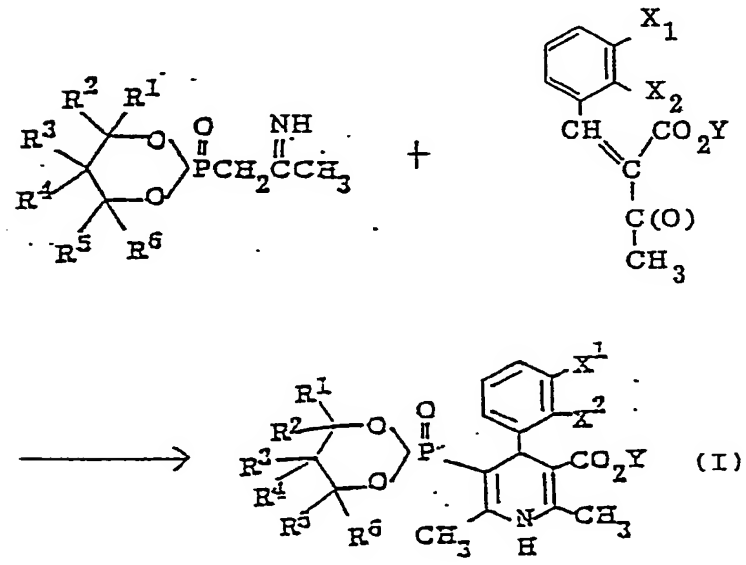
The compound of the formula I may be prepared, also by the following Scheme 3, wherein R^1 to R^6, X^1, X^2 and Y have the same meanings as defined above with respect to the formula I and Z is -O- or $-CH_2-$.

Scheme 3

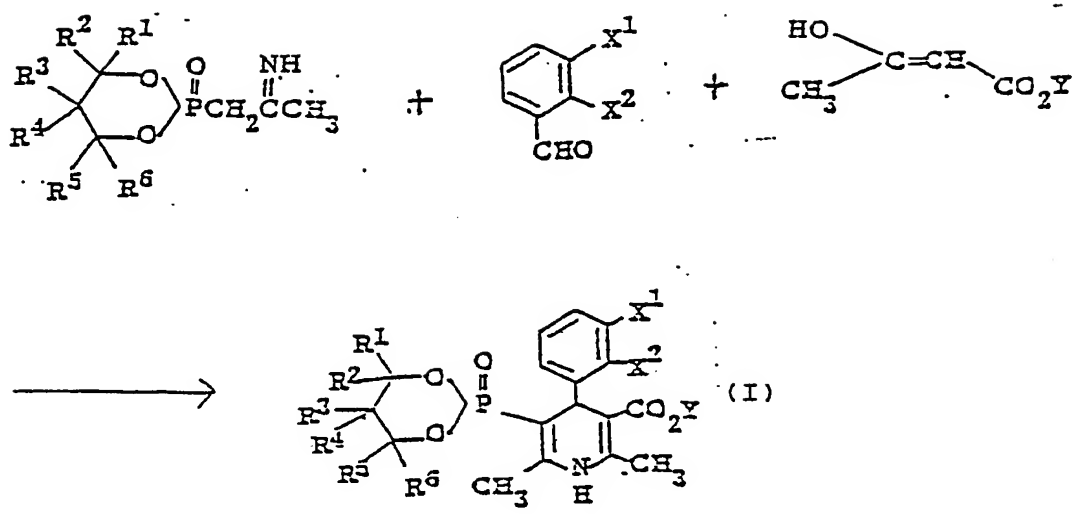
(b) Method wherein the following three starting materials are reacted.



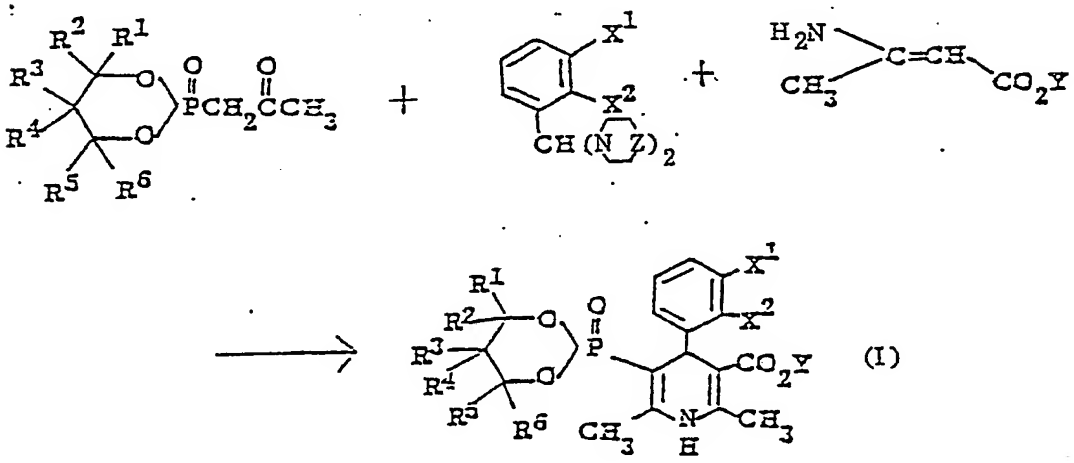
(c) Method wherein the following two starting materials reacted.



(d) Method wherein the following three starting materials reacted.



(e) Method wherein the following four starting materials are reacted in the presence of an α-halogenoalkanoic acid, such as trifluoroacetic acid or monochloroacetic acid.



These reactions may be conducted in inert solvents in accordance with the process for the preparation of the compound of the formula I from compounds of the formulas II and III. Depending upon the solvent for the reaction and the type of the compound of the formula I, a solvate of the formula VI may be formed.

As mentioned above, the compounds of the present invention are not only capable of inhibiting the contraction of smooth muscle and cardiac muscle by the calcium antagonistic effects but also antihypertensively effective when administered orally. Thus, they are useful for the medical treatment of the coronary heart diseases, cerebral diseases or hypertension of mammals.

The oral toxicities of the several compounds of the present invention are unexpectedly low.

The unexpectedly long durations of the antihypertensive action of the several compounds of the present invention have been observed.

Thus, the present invention provides an antihypertensive agent or coronary or cerebral vasodilator composition comprising an effective amount of the compound of the formula I or its pharmaceutically acceptable salt, and a pharmaceutically acceptable diluent or carrier. Such a composition may also be formulated into a veterinary composition by combining the compound of the present invention with a

veterinarily acceptable diluent or carrier.

Such compositions, may be used in the form suitable for oral administration, e.g. tablets or capsules, in the form suitable for transdermal administration, e.g. ointments or plasters, in the form suitable for inhalation, e.g. aerosols or solutions suitable for spraying, in the form suitable for injections, e.g. a sterilized aqueous solution, or in the form of a suppository suitable for use in vagina or rectum.

The compositions of the present invention usually contain the compound of the formula I in an amount of from about 0.1 to about 99.5% by weight, preferably from about 0.5 to about 95% by weight, based on the total weight of the composition.

The compounds of the present invention or the compositions of the present invention may be used in combination with other pharmaceutically or veterinarily active compounds. Further, the composition of the present invention may contain a plurality of the compounds of the formula I.

The daily dose of the compounds of the formula I may be varied depending upon the type and the condition of the desease to be cured and the type of the patient (the age, sex, sensitivity, etc.). In the case of the intravenous administration, the daily dose is usually from 0.0001 to 10 mg, preferably from 0.0005 to 1 mg, of the active ingredient per 1 kg of the body weight. Likewise, in the case of the oral or transdermal administration, the daily dose is usually from 0.001 to 100 mg of the active ingredient per 1 kg of the body weight. Further, the daily dose in the case of the administration in the form of a suppository to e.g. a vagina or rectum, is usually from 0.001 to 200 mg, preferably from 0.005 to 100 mg, of the active ingredient per 1 kg of the body weight. The content of the active ingredient in an aerosol, is usually from 0.1 to 10% by weight, preferably from 0.1 to 2% by weight. Such a daily dose may be divided for administration twice or more times per day.

The above-mentioned compositions containing the compounds of the formula I may be prepared by a conventional method, and a conventional excipient may be incorporated therein.

The present invention will be now described in further detail with reference to Working Examples, Test Examples and various formulations. However, it should be understood that the present invention is by no means restricted by these specific Examples.

EXAMPLES

Test 1: Pharmacological activities of the compounds of the present invention.

(1) Calcium antagonistic effects

10 mm in situ length of taenia caecum of guinea pig was suspended at a tension of 1g in a 20 ml organ bath filled with a physiological salt solution (NaCl: 135 mM, KCl: 5 mM etc.).

This solution was bubbled with a gas mixture of 95% O_2-5% CO_2 and kept at 37°C. Then, the preparation was depolarized by a K+ rich solution (NaCl: 40 mM, KCl: 100 mM). After 10-20 minutes equilibration period, 10 mM of $CaCl_2$ was added to the bathing solution. The contraction was produced, and then the test compound applied cumulatively. The relaxation produced was expressed as percentage of the maximum relaxation produced by 10^{-4} M papaverine, and the concentration of the compound producing 50% relaxation, i.e. ID_{50} (M), was calculated. The values of pID_{50} ($pID_{50} = -\log[ID_{50}]$), are summarized in Table I.

(2) Antihypertensive effects

After oral administration of the test compound dissolved in a H_2O-PEG 400 solvent mixture (H_2O:PEG 400 (v/v) = 1:3) to the male spontaneously hypertensive rat (SHR), the systolic blood pressure was measured at 2, 4, 6 and 8 hours after the administration of the test compounds by a tail cuff method (KN-210-1 made by Natsume Seisakusho). Prior to the measurement, rats were warmed at 50°C for five minutes. The effectively antihypertensive activities were observed also at 8 hours after the administration of the test compounds. The results are summarized in Table 2.

Test 2: Acute toxicity test

ddY mice (♂, 4 weeks old) were divided into groups of three to five mice and the test compound suspended in 0.5% methylcellulose solution was administered orally to the male ddY mice.

After seven days, LD_{50} values were calculated from the dead rats recorded in the individual dosage groups by the method of Litchfield-Wilcoxon. The results are shown in Table I.

Table 1 Calcium antagonistic effect and LD_{50} value of the compound of the present invention.

Test compound	pID_{50}	LD_{50} (mg/kg)
Hydrochloride of Example 1	8.17	>600
Dihydrochloride of Example 2	7.01	>400
Dihydrochloride of Example 3	6.34	>400
Hydrochloride of Example 4	6.90	>300
Hydrochloride of Example 5	-	>300
Hydrochloride of Example 6	6.98	>300
Hydrochloride of Example 7	8.17	>600
Hydrochloride of Example 8	7.21	-
Dihydrochloride of Example 9	7.19	-
Dihydrochloride of Example 10	6.76	-
Hydrochloride of Example 11	6.66	-

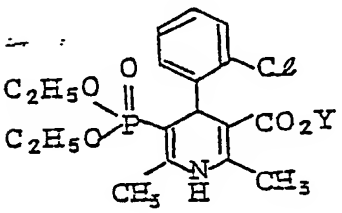
Table 2

Test compound	Dose (mg/kg)	Antihypertensive effect: decrease (%)			
		2(hr)	4	6	8
Comparative compound 1	60	22	9	3	
Comparative compound 2	30	18	7	6	
Compund of formula IV-1-HCl (Hydrochloride of Example 1)	10	14	32	27	15
Dihydrochloride of Example 2	10	15	29	37	26
Dihydrochloride of Example 3	15	19	33	34	29
Hydrochloride of Example 4	20	16	38	37	22
Hydrochloride of Example 5	10	32	40	37	10
Hydrochloride of Example 6	10	12	18	28	15
Hydrochloride of Example 7	15	27	31	34	17
Hydrochloride of Example 8	5	7	23	23	14
Dihydrochloride of Example 9	10	8	17	29	21

Table 2 (continued)

Test compound	Dose (mg/kg)	Antihypertensive effect: decrease (%)			
		2(hr)	4	6	8
Dihydrochloride of Example 10	15	28	36	33	26
Hydrochloride of Example 11	10	15	33	35	30
Dihydrochloride of Example 12	20	15	23	10	1

Structure of Comparative compounds (compounds disclosed in Japanese Unexamined Patent Publication No. 69089/1985)



Comparative compound 1:

$Y=-CH_3$

Comparative compound 2:

$Y=-CH_2CH_2N<^{CH_3}_{CH_2Ph}$

It is evident from the above that the compounds of the present invention are superior to the specific compounds (Comparative compounds) disclosed in Japanese Unexamined Patent Publication No. 69089/1985 in both the activities and the effective period.

(Tests in more detail)

The compound of the formula IV-I-HCl mentioned in Example 15 (which is also hydrochloride of Example 1) has been tested in more detail and it has been found that this compound has pharmaceutically very excellent features as follows.

1. It shows a very slow onset and a long-lasting duration of the hypotensive action.
2. There are no significant changes in the degree of the hypotensive effects by repeated administration for 10 days.
3. It shows high vasculoselectivity against myocardium and almost no effect on contractile force of the heart.
4. It has a low acute toxicity.
5. It shows the diuretic and natriuretic action.

Therefore, the compound (IV-I-HCl) has apparently very excellent features as the antihypertensive agent. The compound of the formula V-I-HCl-C_2H_5OH has activities similar to those of this compound (IV-I-HCl).

Test 3: Antihpertensive effect

Each of the compound of γ-form in Example 15 (Compound A) and Nicardipine hydrochloride was dissolved in the solvent (PEG 400: H_2O (V/V)=2:1) and then administered to male spontaneously hypertensive rats (SHR) via an oral route (10 mg/kg body weight). Following "the test 1: (2) Antihypertensive effect" except the apparatus for measuring the systolic blood pressure was PS-100 made by RIKEN KAIHATSU and that dose group size was 8 rats/group, the systolic blood pressure were measured by a tail-cuff method at the time before the administration, 2, 4, 6, 8, 10 and 24 hours after the administration.

The antihypertensive effect of Compound A and Nicardipine hydrochloride (positive control) have been shown in Figure 1.

Compound A has apparently shown a slow onset and a longer lasting duration of the action than that of Nicardipine hydrochloride as shown in Figure 1.

Test 4: Vasculoselectivity

4-1: Effect on vascular smooth muscles.

The onset of vasodilatory effect of compound A on KCl (50 mM)-induced contraction of the strips of rabbit thoractic aorta was much slower than that of Nifedipine or Nicardipine hydrochloride, and further, the recovery from vasodilation of the strips effected by compound A after being washing out with high -K+ solution was also very slow.

While, $CaCl_2$-induced contraction of the strips in high K+ solution was inhibited by the pre-incubation with Compound A, Nifedipine and Nicardipine hydrochloride. The prolongation of a pre-incubation time with Compound A increased the inhibitory activity.

The pA_2 value were shown in Table 3.

Table 3

Compound	pA_2 Pre-incubation time with the test compound		
	1 hr.	3 hrs.	6 hrs.
Compound A	8.63	9.17	9.33
Nifedipine	8.60	-	-
Nicardipine hydrochloride	9.68	-	9.70

From the results shown in Table 3, it can be said as follows.

Compound A has a strong calcium antagonistic activity on vascular smooth muscle, and it is expected that very slow onset and recovery of vasodilatory effect of Compound A result in a slow onset and a long duration of the antihypertensive action.

4-2: Effects on the myocardium

The atria from male guinea pig were used. The right artium was allowed to been freely, and the left atrium was stimulated electrically. Table 4 shows the percentage of the decrease from initial heart rate (HR) of the right atrium and contractile force (CF) of the left atrium at 3 hours after a application of the test compound.

Table 4

Compound	Heart rate		Contractile force	
	Dose (M)	Decrease (%)	Dose (M)	Decrease (%)
Compound A	10^{-9} 10^{-8}	11.6 60.4	10^{-6}	23.1
Nicardipine hydrochloride	10^{-9} 10^{-8}	11.3 50.0	10^{-7} 10^{-6}	43.5 80.2

From these test results, it can be said as follows.

1. The potency of the negative chronotropic effect of Compound A was almost the same as that of Nicardipine hydrochloride. On the other hand, the potency of the negative inotropic effect of Compound A was over 10 times less than Nicardipine hydrochloride.
2. Compound A has high vasculoselectivity and almost no effect of CF of the heart.

Test 5: Acute toxicity

Male ddY strain mice aged 4 weeks [ddY strain mice] and male Sprague-Dawley rats aged 6 weeks [SD strain rats] were used. The test compound suspended in 0.5% methylcellulose solution was administered to mice and rats via an oral route. These animals were examined for 7 days after administration. The results are shown in Table 5.

Table 5

Test animals	Dose (mg/kg)	Test compounds	
		Compound A Dead animals/ tested animals	Nicardipine hydrochloride Dead animals/ tested animals
ddY strain mice	300	0/3	0/3
"	424	0/3	1/3
"	600	0/3	3/3
SD strain rats	600	0/5	2/5
"	1200	0/5	2/5
"	2400	0/5	5/5

As shown in Table 5, Compound A is apparently less toxic than Nicardipine hydrochloride.

Test 6: Diuretic Effect

Male SHR (10-11 weeks old) fasted for 18 hr. were used. Just after p.o. administration of the test compounds, they received 25 ml/kg of 0.9% NaCl solution orally. Then, each rat was placed in a metabolism cage, and the urine was collected for 10 hr. Urinary electrolytes (Na+) were measured with a flame photometer (FPF-3A made by Hiranuma Seisakusho). The results are shown in Table 6.

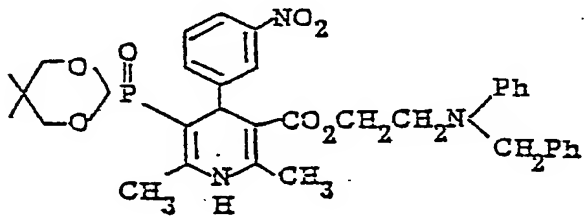
Table 6

Test Compound	Dose (mg/kg)	Volume of the urine (ml/rat)	Na content in the urine (mEq/rat)
Control	-	4.7	0.73
Compound A	10	7.9	1.02
"	20	15.3	1.25
Furosemide	20	7.7	1.02

As shown in Table 6, the diuretic and natriuretic effects of Compound A are stronger than those of Furosemide, a diuretic.

EXAMPLE 1

Synthesis of 2-(N-benzyl-N-phenylamino)ethyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(3-nitrophenyl)pyridine-3-carboxylate



EXAMPLE 1-1

[Method a]

14.7 g of 2.2-dimethylpropylene α-(3-nitrobenzylidene)acetonylphosphonate and 13.4 g of 2-(N-benzyl-N-phenylamino)ethyl 3-aminocrotonate were dissolved in 50 ml of toluene, and the solution was refluxed for 10 hours. Then, the precipitate was collected by filtration and was recrystallized from ethyl acetate, whereby the above-identified compound was obtained as yellow crystal (mp 155-156° C). In a similar manner, compounds of Example 2 to 12 were obtained. The characteristics and the mass spectral data of the compounds thus obtained are shown in Table 7.

EXAMPLE 1-2

[Method b]

2.1 g of 2,2-dimethylpropylene acetonylphosphonate, 1.5 g of 3-nitrobenzaldehyde and 3.1 g of 2-(N-benzyl-N-phenylamino)ethyl 3-aminocrotonate are dissolved in toluene, and the solution is refluxed. Then, the solvent is distilled off under reduced pressure, and the residue is purified by silica gel column chromatography, followed by recrystallization from ethyl acetate, whereby the above-identified compound is obtained.

EXAMPLE I-3

[Method c]

2.1 g of 2,2-dimethylpropylene 2-amino-1-propenylphosphonate and 4.4 g of 2-(N-benzyl-N-phenylamino)ethyl α-(3-nitrobenzylidene)acetoacetate are dissolved in toluene, and the solution is refluxed. Then, the solvent is distilled off under reduced pressure, and the residue is purified by silica gel column chromatography, followed by recrystallization from ethyl acetate, whereby the above-identified compound is obtained.

EXAMPLE I-4

[Method d]

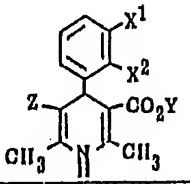
2.1 g of 2,2-dimethylpropylene 2-amino-1-propenylphosphonate, 1.5 g of 3-nitrobenzaldehyde and 3.1 g of 2-(N-benzyl-N-phenylamino)ethyl acetoacetate are dissolved in toluene, and the solution is refluxed. Then, the solvent is distilled off under reduced pressure, and the residue is purified by silica gel column chromatography, followed by recrystallization from ethyl acetate, whereby the above-identified compound is obtained.

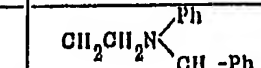
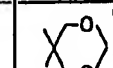
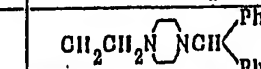
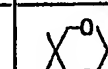
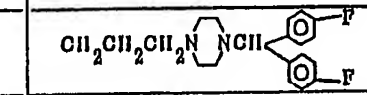
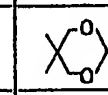
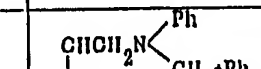
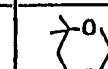
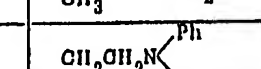
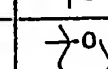
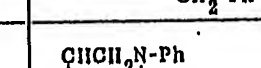
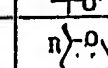
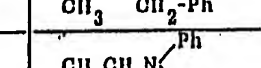
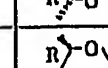
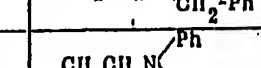
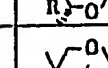
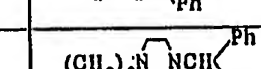
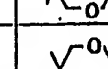
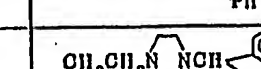
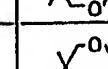
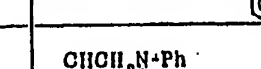
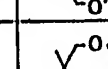
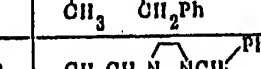
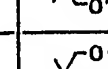
EXAMPLE I-5

[Method e]

2.1 g of 2,2-dimethylpropylene actonylphosphonate, 3.1 g of 4,4'-((3-nitrophenyl)methylene)bismorpholine and 3.1 g of 2-(N-benzyl-N-phenylamino)ethyl 3-aminocrotonate is dissolved in toluene, and 2.3 g of trifluroacetic acid is added to the solution with dropwise for 10 minutes, following the solution was refluxed for 2 hours. Then, the solution is washed by water and dried with Na_2SO_4. Then, the solvent is distilled off under reduced pressure, and the residue is purified by silica gel column chromatography, followed by recrystallization from ethyl acetate, whereby the above-identified compound is obtained.

Table 7



Example No.	X^1	X^2	Y	Z	Yield (%)	Characteristics (mp, °C)	MS, m/e (Intensity ratio)
1	NO_2	H			45	Yellow solid (155-156)	106(61), 200(100), 631(7, M^+)
2	Cl	Cl			60	Yellow solid (206-207)	44(100), 167(32), 408(5)
3	Cl	Cl			55	Yellow amorphous	126(81), 203(100), 301(38), 773(20, M^+)
4	NO_2	H			40	Yellow oily substance	106(100), 495(5), 650(3), 673(2, M^+)
5	NO_2	H			69	Yellow oily substance	81(100), 106(93), 481(15)
6	Cl	Cl			46	Yellow oily substance	91(67), 223(100), 609(2, M^+)
7	NO_2	H			81	Yellow oily substance	180(50), 209(100), 631(11, M^+)
8	Cl	Cl			68	Pale yellow solid (131)	182(29), 195(100), 640(5, M^+)
9	Cl	Cl			74	Pale yellow solid (158)	125(100), 167(29), 428(39), 737(18, M^+)
10	Cl	Cl			67	Pale yellow solid (141)	203(100), 300(44), 759(12, M^+)
11	Cl	Cl			84	Yellow oily substance	223(100), 408(5), 668(2, M^+)
12	H	$OCHF_2$			75	Colorless solid (214)	167(100), 278(63), 426(54), 721(40, M^+)

EXAMPLE 13

13 g of 2,2-dimethylpropylene α-(3-nitrobenzylidene)-acetonylphosphonate and 11.9 g of 2-(N-benzyl-N-phenylamino)ethyl 3-aminocrotonate were dissolved in 100 g of toluene, and the solution was refluxed for 2 hours while removing formed water by azeotropic dehydration. The reaction solution was cooled to room temperature, whereby a solvate of 2-(N-benzyl-N-phenylamino)ethyl 5-(2,2-dimethyl propylenedioxyphosphinyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylate (I-1) with one molecule of toluene (VI-1-Toluene) was obtained as crystals.

Yellow crystals, amount: 23.6 g (yield: 85%)

The compound of the formula I-1 was found to form a solvate also with benzene.

When these solvates were recrystallized from ethyl acetate or ethanol, the compounds free from solvent (toluene or benzene) were obtained. The melting point and the NMR spectrum of the compound free from solvent are as follows.

mp: 156-158°C

NMR (CDCl3):

δ: 0.66(3H, s), 0.99(3H, s), 2.25(3H, s), 2.3(3H, d, J=2.5Hz), 3.5-3.7(4H, m), 4.1-4.4(4H, m), 4.51(2H, s), 4.9(1H, d, J=10.9Hz), 6.47(1H, d, J=4.2Hz), 6.67(3H, m), 7.1-7.35(8H, m), 7.58(1H, d, J=6.6Hz), 7.96(1H, m), 8.07(1H, t, J=1.9Hz)

EXAMPLE 14

193.1 g of the toluene solvate (VI-1-Toluene) obtained by the method following the Example 13 was dissolved under heating in 996 g of ethanol, and 51 g of a 21% hydrogen chloride-ethanol solution was added thereto. The mixture was cooled to room temperature, whereby 185.2 g (yield: 97.2%) of a solvate of the hydrochloride with 1 mol of ethanol (V-1-HCl-C_2H_5OH) was obtained.

Yellow crystals, mp: 149-155°C (decomposed)

EXAMPLE 15

135 g of the toluene solvate (VI-1-Toluene) obtained in Example 13 was dissolved under heating in 783 g of acetone, and 21.4 g of 35% hydrochloric acid was slowly dropwise added thereto. After the completion of the dropwise addition, the reaction solution was cooled to room temperature, whereby 121.6 g (yield: 97.6%) of the hydrochloride (γ-form of IV-1-HCl) was obtained.

Greenish yellow needle-like crystals (γ-form) mp: 149-156°C (decomposed)

The compound of the formula IV-1-HCl was dissolved in ethanol/chloroform = 1/9 (v/v), and the solvent was distilled off. The residue was dissolved in acetone and left to stand still at room temperature, whereby the hydrochloride of the formula IV-1-HCl having a different crystal form (α-form) was obtained. The α-form was capable of being converted to a different crystal form (β-form) by heating (at 70°C).

EXAMPLE 16

7.24 g of the toluene solvate (VI-1-Toluene) obtained in Example 13 was dissolved under heating in 30 g of acetonitrile, and 2 g of 35% hydrochloric acid was added thereto. The mixture was cooled to room temperature and left to stand for 5 hours, whereby 4.52 g (yield: 63.8%) of a solvate of the hydrochloride of the compound of the formula IV-1-HCl with 1 mol of acetonitrile (V-1-HCl-CH_3CN) was obtained.

Yellow crystals, mp: 149-156°C (decomposed)

When this compound was heated at 70°C, acetonitrile was removed to obtain crystals of β-form.

Now, examples will be given for various formulations containing the compound of the formula I. In the following Formulation Examples, Compound A is as mentioned above, γ-form of hydrochloride in Example 15.

Tablets

Composition (1,000 tablets)

Compound A or hydrochloride of the compound of the Example 2	20.0 (g)
Lactose	70.0
Corn starch	25.0
Crystal cellulose powder	25.0
Polyvinyl pyrrolidone	8.0
Magnesium stearate	2.0
	150.0

Each amount of the above ingredient was introduced into a twin shell blender and uniformly mixed. This mixture was tableted by a direct compression method to obtain tablets having a weight of 150 mg per tablet.

Capsules

Composition (1,000 capsules)

Compound A or hydrochloride of the Compound of the Example 2	20 (g)
Corn starch	65
Crystal cellulose powder	60
Magnesium stearate	5
	150

Each amount of the above ingredient was introduced into a twin shell blender and uniformly mixed. Each 150 mg of the mixture was packed in a hard gelatin capsule.

Powder

Composition:

Compound A or hydrochloride of the compound of the Example 2	1.0 (g)
Lactose	88.0
Crystal cellulose powder	10.0
Methyl cellulose	1.0
	100.0

Each amount of the above ingredient was introduced into a twin shell blender and uniformly mixed to obtain a powder.

Syrup

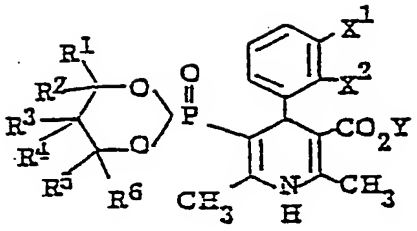
Composition (2% syrup):

Compound A or hydrochloride of the compound of the Example 2	2.0 (g)
Sugar	30.0
Glycerin	5.0
Flavoring agent	0.1
96% ethanol	10.0
Methyl p-hydroxybenzoate	0.03
Purified water	to make 100.0 g

The sugar and the hydrochloride of the compound of Example I were dissolved in 50 g of warm water, and after cooling the solution, a solution of the flavoring agent in glycerin and ethanol was added. Then, water was added to this mixture to bring the total amount to 100.0 g.

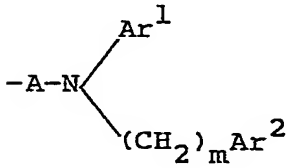
Claims

I. A compound of the formula:

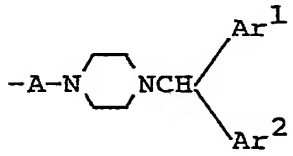


(I)

wherein each of R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different, is hydrogen or C_1-C_4 alkyl; one of X^1 and X^2 is nitro, fluorine, chlorine, difluoromethoxy or trifluoromethyl and the other is hydrogen, or both of X^1 and X^2 are chlorine; and Y is



wherein A is C_2-C_6 alkylene, each of Ar^1 and Ar^2 which may be the same or different, is phenyl which may be substituted by chlorine, fluorine or C_1-C_3 alkoxy, and m is an integer of from 0 to 4, or Y is



wherein A, Ar^1 and Ar^2 are as defined above when X^1 is hydrogen and X^2 is difluoromethoxy or when both X^1 and X^2 are chlorine; or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt.

2. The compound of Claim 1, wherein one of X^1 and X^2 is nitro or chlorine and the other is hydrogen, or both of X^1 and X^2 are chlorine.

3. The compound of Claim 2, wherein each of R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different, is hydrogen or methyl.

4. The compound of Claim 3, wherein A is $-CH_2CH_2-$, $-(CH_2)_3-$ or $-CH(CH_3)CH_2-$, and m is one.

5. The compound of Claim 4, wherein each of Ar^1 and Ar^2 which may be the same or different, is phenyl or p-fluorophenyl.

6. The compound of Claim 5, wherein $-C(R^1)(R^2)C(R^3)(R^4)C(R^5)(R^6)-$ is $-CH_2C(CH_3)_2CH_2-$, $-C(CH_3)_2CH_2C(CH_3)_2-$ or $-CH(CH_3)CH_2CH(CH_3)-$.

7. The compound of Claim 1, wherein X^1 is nitro, X^2 is hydrogen, or both of X^1 and X^2 are chlorine; $-C(R^1)(R^2)C(R^3)(R^4)C(R^5)(R^6)-$ is $-CH_2C(CH_3)_2CH_2-$, $-C(CH_3)_2CH_2C(CH_3)_2-$ or $-CH(CH_3)CH_2CH(CH_3)-$; A is $-CH(CH_3)CH_2-$ or $-CH_2CH_2-$;

and Y= is $-A-N<^{\text{phenyl}}_{CH_2\ \text{phenyl}}$.

8. The compound of Claim 7, wherein X^1 is nitro, X^2 is hydrogen.

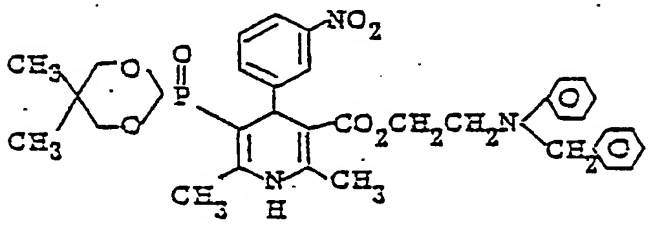
9. The compound of Claim 1, wherein X^1 is hydrogen, X^2 is difluoromethoxy or both X^1 and X^2 are chlorine;
$-C(R^1)(R^2)C(R^3)(R^4)C(R^5)(R^6)-$ is $-C(CH_3)_2CH_2C(CH_3)_2-$, $-CH(CH_3)CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2CH_2-$;
A is $-CH(CH_3)CH_2-$, $-CH_2CH_2-$ or $CH_2CH_2CH_2-$;
Ar^1 and Ar^2, which may be the same or different, is phenyl or p-fluorophenyl; and

Y is -A-N⟨ ⟩NCH⟨Ar^1 / Ar^2 .

10. The compound of Claim 1, wherein both X^1 and X^2 are chlorine:
$-C(R^1)(R^2)C(R^3)(R^4)C(R^5)(R^6)-$ is $-CH_2C(CH_3)_2CH_2-$;
A is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;
Ar^1 and Ar^2 is phenyl or p-fluorophenyl; and

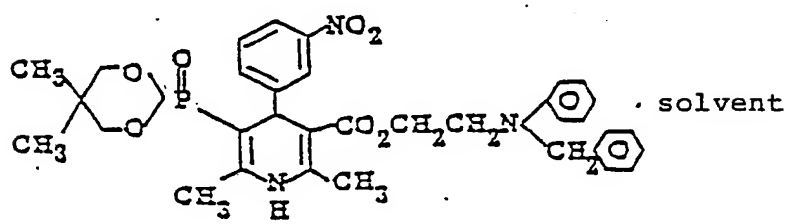
Y is -A-N⟨ ⟩NCH⟨Ar^1 / Ar^2 ..

11. The compound of Claim 1, having the formula:



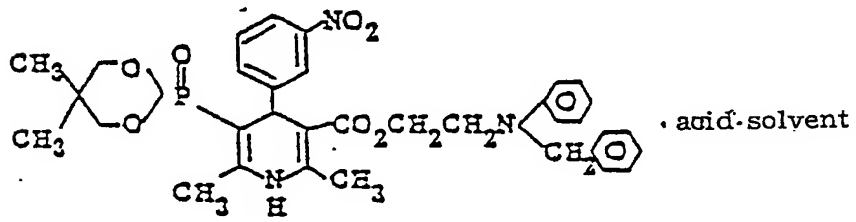
or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 1, having the formula:



wherein solvent is benzene or toluene.

13. Solvate of a pharmaceutically acceptable salt of the compound of Claim 1, having the formula:

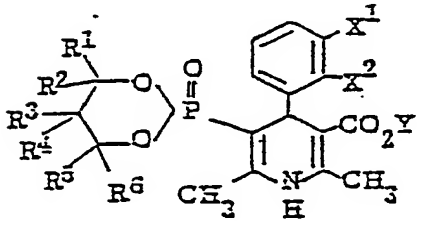


wherein solvent is ethanol or acetonitrile.

14. The compound of Claim 1, which is 2-(4-diphenylmethyl-1-piperazinyl)ethyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate, 3-(4-bis(4-fluorophenyl)-methyl-1-piperazinyl)propyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate, 1-methyl-2-(N-benzyl-N-phenylamino)ethyl 5-(1,1,3,3-tetramethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(3-nitrophenyl)-pyridine-3-carboxylate,

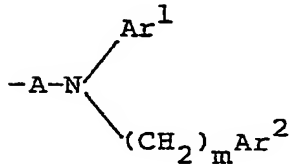
2-(N-benzyl-N-phenylamino)ethyl 5-(1,1,3,3-tetramethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(3-nitrophenyl)-pyridine-3-carboxylate, 1-methyl-2-(N-benzyl-N-phenylamino)ethyl 5-(1(R), 3(R)-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate, 2-(N-benzyl-N-phenylamino)ethyl 5-(1(R), 3(R)-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(3-nitrophenyl)-pyridine-3-carboxylate, 2-(N,N-diphenylamino)ethyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichloro phenyl)-pyridine-3-carboxylate, 3-(4-diphenylmethyl-1-piperazinyl)propyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate, 2-(4-bis(4-fluorophenyl)methyl-1-piperazinyl)propyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate, 1-methyl-2-(N-benzyl-N-phenylamino)ethyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)-pyridine-3-carboxylate or 2-(4-diphenylmethyl-1-piperazinyl)ethyl 5-(2,2-dimethylpropylenedioxyphosphinyl)-2,6-dimethyl-1,4-dihydro-4-(2-difluoromethoxyphenyl)-pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt.

15. A process for producing a compound represented by the formula:

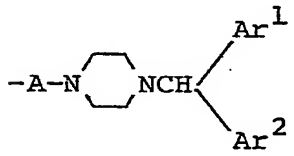


(I)

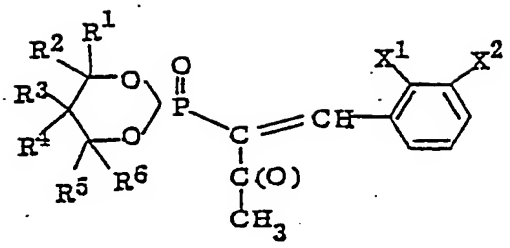
wherein each of R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different, is hydrogen or C_1-C_4 alkyl; one of X^1 and X^2 is nitro, fluorine, chlorine, difluoromethoxy or trifluoromethyl and the other is hydrogen, or both of X^1 and X^2 are chlorine; and Y is



wherein A is C_2-C_6 alkylene, each of Ar^1 and Ar^2 which may be the same or different, is phenyl which may be substituted by chlorine, fluorine or C_1-C_3 alkoxy, and m is an integer of from 0 to 4, or Y is

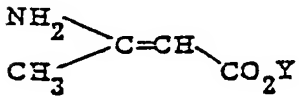


wherein A, Ar^1 and Ar^2 are as defined above when that both X^1 and X^2 are chlorine; or a pharmaceutically acceptable salt thereof; or a solvate of the compound or the salt, which comprises reacting a compound represented by the formula:



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, X^1 and X^2 are as defined above, with a compound represented by the formula:



(III)

wherein Y is as defined above, optionally converting the resulting compound of the formula I to its pharmaceutically acceptable salt and optionally converting the compound of the formula I or the salt to a solvate.

16. An antihypertensive, coronary or cerebral vasodilator composition comprising

(a) an antihypertensive, coronary or cerebral vasodilator effective amount of the compound of Claim 1; and

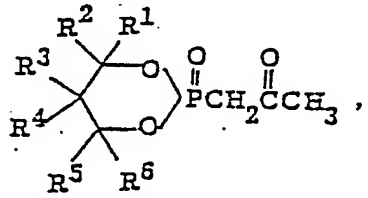
(b) a pharmaceutically acceptable diluent or carrier.

17. A method of treating hypertension in a subject in need of such treatment comprising administering to the subject an antihypertensive effective amount of the compound of Claim 1 to produce such effect.

18. A method of producing coronary vasodilation in a patient in need of such treatment comprising administering to the patient a coronary vasodilating effective amount of the compound of Claim 1 to produce such effect.

19. A method of producing cerebral vasodilation in a patient in need of such treatment comprising administering to the patient a cerebral vasodilating effective amount of the compound of Claim 1 to produce such effect.

20. A process for producing a compound of the formula I as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt, which comprises reacting the following three starting materials



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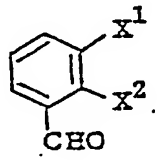
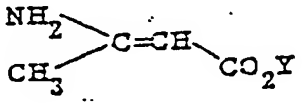
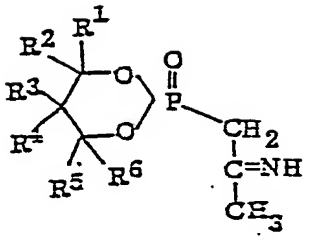


and

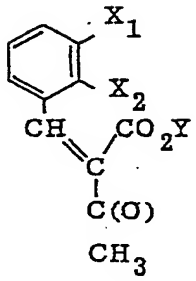


wherein R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and Y are as defined in Claim 1, optionally converting the resulting compound of the formula I to its pharmaceutically acceptable salt, and optionally converting the compound of the formula I or the salt to a solvate.

21. A process for producing a compound of the formula I as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt, which comprises reacting the following two starting material

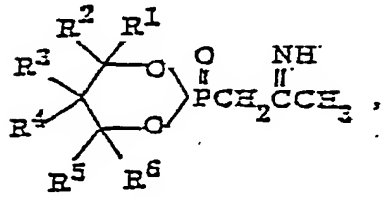


and



wherein R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and Y are as defined in Claim I, optionally converting the resulting compound of the formula I to its pharmaceutically acceptable salt, and optionally converting the compound of the formula I or the salt to a solvate.

22. A process for producing a compound of the formula I as defined in Claim I, or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt, which comprises reacting the following three starting material



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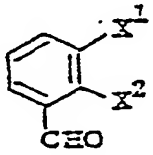
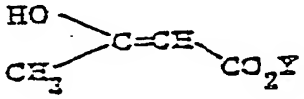
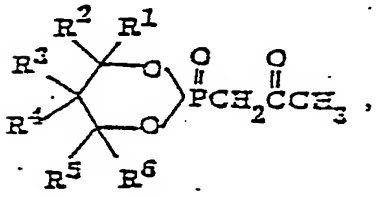


and



wherein R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and Y are as defined in Claim I, optionally converting the resulting compound of the formula I to its pharmaceutically acceptable salt, and optionally converting the compound of the formula I or the salt to a solvate.

23. A process for producing a compound of the formula I as defined in Claim I, or a pharmaceutically acceptable salt thereof, or a solvate of the compound or the salt, which comprises reacting the following three starting material in the presence of an α-halogenoalkanoic acid



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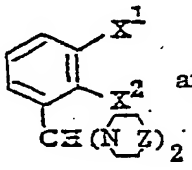
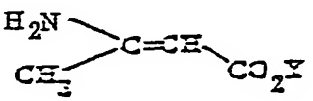
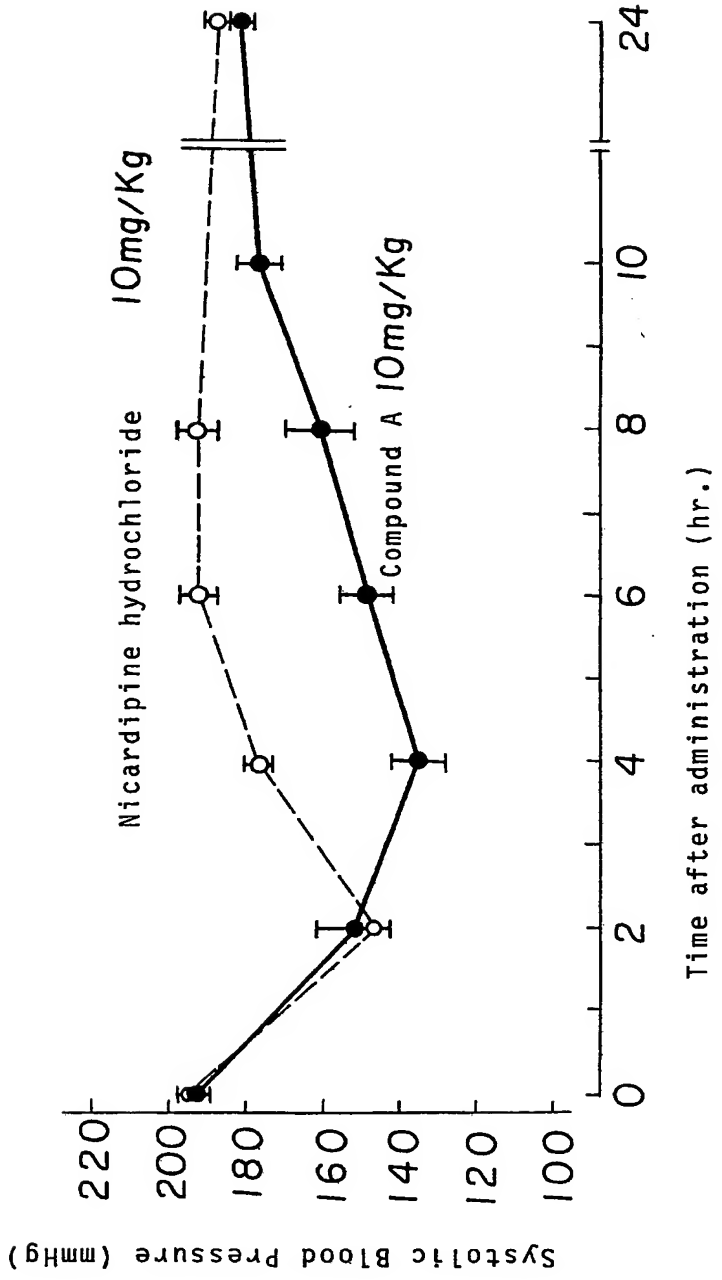


and



wherein R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and Y are as defined in Claim I and Z is -O- or $-CH_2-$, optionally converting the resulting compound of the formula I to its pharmaceutically acceptable salt, and optionally converting the compound of the formula I or the salt to a solvate.

FIGURE 1


Nicardipine hydrochloride 10mg/Kg
Compound A 10mg/Kg
Systolic Blood Pressure (mmHg)
220
200
180
160
140
120
100
0
2
4
6
8
10
24
Time after administration (hr.)

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 87 10 0602

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,Y	EP-A-0 141 222 (NISSAN CHEMICAL INDUSTRIES LTD) * Claims * ---	1,23	C 07 F 9/65 A 61 K 31/675
D,Y	EP-A-0 141 221 (NISSAN CHEMICAL INDUSTRIES LTD) * Claims * -----	1-3	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 F 9/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	01-04-1987	BESLIER L.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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